NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC) GUIDELINE SYNTHESIS

SCREENING FOR PROSTATE CANCER

GUIDELINES BEING COMPARED

1. **American College of Preventive Medicine (ACPM)**. Screening for prostate cancer in U.S. men. Am J Prev Med 2008 Feb;34(2):164-70. [60 references]
2. **American Urological Association (AUA)**. Prostate-specific antigen best practice statement: 2009 update. Linthicum (MD): American Urological Association Education and Research, Inc.; 2009. 82 p. [264 references]
3. **U.S. Preventive Services Task Force (USPSTF)**. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008 Aug 5;149(3):185-91. [19 references]

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AREAS OF AGREEMENT AND DIFFERENCE

A direct comparison of the American College of Preventive Medicine (ACPM), American Urological Association (AUA), and U.S. Preventive Services Task Force (USPSTF) recommendations for screening for prostate cancer is provided in the tables below.

Areas of Agreement

Screening in Average-Risk, Asymptomatic Men

All of the organizations emphasize the considerable controversy surrounding screening due to the lack of conclusive evidence that screening can reduce mortality from prostate cancer. All of the groups also address the clear potential that screening may increase treatment-related morbidity. The groups agree that there is insufficient evidence to recommend routine screening for prostate cancer in any age group, and that the decision to undergo screening should be an

individualized, informed decision on the part of the patient in consultation with his physician. There is overall agreement that clinicians should inform men of the potential benefits, known risks (including overdetection and overtreatment), as well as the limits/gaps in current evidence. These factors, in conjunction with the patient's personal preferences and age/life expectancy, should be taken into consideration in the collaborative decision-making process. ACPM notes that discussion about screening should occur annually, during the routine periodic examination, or in response to a request by the patient.

If the decision to screen is made, there is overall agreement that while the PSA test is more sensitive than the DRE, the DRE is useful and should be performed as well. AUA and USPSTF also address variations of PSA screening proposed to improve detection of "clinically significant" prostate cancer cases, including age-adjusted PSA cutpoints, free/total PSA ratio, complexed PSA, PSA kinetics (e.g., PSAV, PSADT, PSA slope), and PSA density. Neither group recommends their use, however. According to USPSTF, no evidence suggests that any of these testing strategies improves health outcomes. AUA states that because of potential tradeoffs between sensitivity and specificity, there is at present no consensus on optimal strategies for using the different modifications of PSA testing.

Screening in High-Risk Men

Two groups, ACPM and USPSTF, address screening in men at increased risk. While ACPM falls short of making an explicit recommendation for screening in high-risk men, they acknowledge that screening for prostate cancer among African-American men and those with a family history of prostate cancer has the potential to detect treatable forms of disease that are more likely to occur in these groups than in the general population. They add that while the usual age for prostate cancer screening is between 50 to 70 years in average risk men, it has been suggested that those who are at high risk may benefit from earlier screening beginning at age 45, while higher-risk men (those with two or more first-degree relatives with prostate cancer before age 65) be screened at age 40. They continue to note, however, that further studies are needed to establish the efficacy and optimal age at which prostate cancer screening should be initiated in these high-risk population groups.

Similar to ACPM, USPSTF makes no formal recommendation regarding screening in high-risk populations. They acknowledge that older men, African-American men, and men with a family history of prostate cancer are at increased risk for diagnosis and death from prostate cancer, but note that unfortunately, the gaps in the evidence regarding potential benefits of screening also apply to these men.

Areas of Difference

Screening in Average-Risk, Asymptomatic Men

While none of the groups recommend routine screening for prostate cancer, AUA nonetheless provides recommendations for men to whom screening should be offered, recommending screening with PSA and DRE be offered to asymptomatic, well-informed men $\geq$ 40 years of age with a life expectancy of at least 10 years.

With regard to screening in older men, there is overall agreement that screening men with a life expectancy of less than 10 years is discouraged. USPSTF, estimating the age at which the average American male has ten years or less life expectancy (age 75), is the only group to explicitly recommend against screening men age 75 years or older. AUA, however, states that a physician should assess the individual patient's health status to determine the appropriateness of PSA testing at any given age. Referring to the USPSTF recommendation against screening in men $\geq$ 75, AUA cautions that individualization of this recommendation is warranted, especially in men with excellent health, absence of comorbidities, and family longevity. Additionally, AUA adds, there must be a distinction made between screening for prostate cancer and treatment of prostate cancer. Diagnosis of prostate cancer in this age group may be informative for a man's overall health but may never require treatment beyond active surveillance. Conversely, men with aggressive prostate cancer in this age group should not be denied the opportunity for the diagnosis and treatment which could affect their length and quality of life.

COMPARISON OF RECOMMENDATIONS	
SCREENING FOR PROSTATE CANCER **Abbreviations** **Back to TOC**	
ACPM (2008)	**Recommendation of the ACPM** The ACPM concludes that there is currently insufficient evidence to recommend routine population screening with DRE or PSA, concurring with the USPSTF recommendation. The College is in agreement with the American College of Physicians (ACP) that men should be given information about the potential benefits and harms of screening and limits of current evidence in order to make an informed decision about screening. Discussion about screening should occur annually, during the routine periodic examination, or in response to a request by the patient. The effectiveness of prostate cancer screening is questionable in elderly men with competing co-morbidities and men with life expectancies of less than 10 years. Ultimately, a man should be allowed to make his own choice about screening, in consultation with his physician, taking into consideration personal preferences and life expectancy. If the patient prefers to defer to the clinician or is unable to make a decision regarding screening, then testing should not be offered as long as the patient understands the benefits, potential limitations, and adverse effects associated with screening. Key points that should be communicated during the patient encounter regarding prostate cancer screening are listed in Table 1 of the original guideline document. Pending resolution of ongoing controversies, screening for prostate cancer among African-American men and those with a family history

	of prostate cancer has the potential to detect treatable forms of disease that are more likely to occur in these groups than in the general population. While the usual age for prostate cancer screening is between 50 to 70 years in average risk men, it has been suggested that those who are at high risk may benefit from earlier screening beginning at age 45, while higher-risk men (those with two or more first-degree relatives with prostate cancer before age 65) be screened at age 40. Granted that prostate cancer is more likely to be found in high-risk men, issues pertaining to tumor grade have yet to be resolved (that is, optimal grade of tumor that a screening test should detect to confer a benefit in survival or morbidity), and there is still no evidence establishing effectiveness of screening in high-risk men. In the meantime further studies are needed to establish the efficacy and optimal age at which prostate cancer screening should be initiated in these high-risk population groups.
AUA (2009)	**<u>The Use of PSA for Early Detection of Prostate Cancer</u>** Given the uncertainty that PSA testing results in more benefit than harm, a thoughtful and broad approach to PSA is critical. Patients need to be informed of the risks and benefits of testing before it is undertaken. The risks of overdetection and overtreatment should be included in this discussion. Because there is now evidence from a RCT regarding a mortality decrease associated with PSA screening, the AUA is recommending PSA screening, as proposed in this document, for well-informed men who wish to pursue early diagnosis. The AUA recommends that all discussions of treatment options include active surveillance as a consideration, since many screen-detected prostate cancers may not need immediate treatment. **Men Who Wish to Be Screened for Prostate Cancer Should Have Both a PSA Test and a DRE**. While PSA level measurement is currently the best single test for early prostate cancer detection, DRE can also identify men with the disease. Evidence from three uncontrolled studies suggests that combining both tests improves the overall rate of prostate cancer detection when compared to either test alone. Recent evidence from the ERSPC found that DRE did not improve prostate cancer screening over PSA testing alone, however. Finally, DRE examination may be a barrier to screening for some. Transrectal ultrasonography adds no additional information to the combination of PSA testing and DRE as screening tests, but is useful in biopsy guidance and staging. **Note**: Refer to the original guideline document for discussion of factors that can affect PSA levels and that should be considered in the interpretation of results. **For Patients Choosing to Undergo PSA Testing, Several**

Important Questions Arise Regarding the PSA Test's Performance for Detection of Prostate Cancer.

Note: Refer to the original guideline document for a discussion of modifications of PSA testing.

All four methods — age-adjusted PSA, free/total PSA ratio, complexed PSA, and PSA/TZPSAD density — can be used to improve the sensitivity (detect more cancers) and/or specificity (avoid unnecessary biopsies) of PSA testing. To what extent such methods will do either is heavily dependent on the cut-points used and the subset of PSA levels to which they are applied.

The use of risk assessment tools can also be applied to prostate cancer screening and help determine the need for biopsy. Several nomograms help estimate a man's risk of harboring prostate cancer at different PSA levels, and recently a risk calculator was published that uses individual patient characteristics to predict his likelihood of having prostate cancer detected on biopsy. These tools take into account multiple patient variables to help determine the need for prostate biopsy, rather than relying on an arbitrary threshold value, and facilitate discussion of a patient's individualized risk.

Because of potential trade-offs between sensitivity and specificity, there is at present no consensus on optimal strategies for using the different modifications of PSA testing.

The Decision to Use PSA for the Early Detection of Prostate Cancer Should Be Individualized. Patients Should Be Informed of the Known Risks and the Potential Benefits.

Decisions regarding early detection of prostate cancer should be individualized, and benefits and consequences should be discussed with the patient before PSA testing occurs. Not all men are appropriate candidates for screening efforts for this disease. Ideally, physicians should consider a number of factors, including patient age and comorbidity, as well as preferences for the relevant potential outcomes. Screening in men with less than a 10-year life expectancy, either due to age or comorbidity, is discouraged.

Early Detection and Risk Assessment of Prostate Cancer Should Be Offered to Asymptomatic Men 40 Years of Age or Older Who Wish to be Screened with an Estimated Life Expectancy of More Than 10 Years.

One way to identify the high-risk group of men with a PSA level above the median value in their 40s is to obtain a baseline PSA level at age 40, and then to determine future screening intervals based upon this number. Men in their 40s with a PSA value above the median (0.6 to 0.7 ng/mL) are at higher risk for prostate cancer.

	Because of the long natural history of prostate cancer and the ability of PSA screening to uncover most cases of advanced life-threatening cancer at the initial screen, frequent screening will contribute to the cumulative risk of undergoing a biopsy and appears unnecessary for most men. Rescreening intervals should be based on the results of the PSA test since the future risk of prostate cancer is closely related to the PSA level. Because of the long natural history of most prostate cancers and competing causes of death, the benefits of screening may decline rapidly with age. A physician should assess the individual patient's health status to determine the appropriateness of PSA testing at any given age. Recently, the USPSTF issued guidelines which recommend against screening men over age 75. While this recommendation estimates the age at which the average American male has ten years or less life expectancy, individualization of this recommendation is warranted, especially in men with excellent health, absence of comorbidities, and family longevity. Additionally, there must be a distinction made between screening for prostate cancer and treatment of prostate cancer. Diagnosis of prostate cancer in this age group may be informative for a man's overall health but may never require treatment beyond active surveillance. Conversely, men with aggressive prostate cancer in this age group should not be denied the opportunity for the diagnosis and treatment which could affect their length and quality of life.
USPSTF (2008)	**Summary of Recommendation and Evidence** • The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of prostate cancer screening in men younger than age 75 years. **This is an I statement.** • The USPSTF recommends against screening for prostate cancer in men age 75 years or older. **This is a grade D recommendation.** **Clinical Considerations** **Patient Population under Consideration** This recommendation applies to men in the general U.S. population. **Risk Assessment** Older men, African-American men, and men with a family history of prostate cancer are at increased risk for diagnosis and death from prostate cancer. Unfortunately, the previously described gaps in the evidence regarding potential benefits of screening also apply to

	these men. **Screening Tests** The PSA test is more sensitive than the DRE for detecting prostate cancer. The conventional PSA screening cut-point of 4.0 micrograms/L detects many prostate cancer cases; however, some early cases of prostate cancer will be missed by this cut-point. Using a lower cut-point to define an abnormal PSA detects more cases of cancer. The proportion of cancer cases detected by lower cut-points that would ever become clinically apparent is unknown; lower cut-points would label many more men as potentially having cancer. For example, lowering the PSA cut-point to 2.5 micrograms/L would more than double the number of U.S. men between 40 and 69 years of age with abnormal results. Variations of PSA screening, including the use of age-adjusted PSA cut-points, free PSA, PSA density, PSA velocity, PSA slope, and PSA doubling time, have been proposed to improve detection of "clinically important" prostate cancer cases. However, no evidence suggests that any of these testing strategies improves health outcomes. **Suggestions for Practice** Given the uncertainties and controversy surrounding prostate cancer screening in men younger than age 75 years, a clinician should not order the PSA test without first discussing with the patient the potential but uncertain benefits and the known harms of prostate cancer screening and treatment. Men should be informed of the gaps in the evidence and should be assisted in considering their personal preferences before deciding whether to be tested. **Screening Intervals** The yield of screening in terms of cancer cases detected declines rapidly with repeated annual testing. If screening were to reduce deaths, PSA screening as infrequent as every 4 years could yield as much of a benefit as annual screening.

STRENGTH OF EVIDENCE AND RECOMMENDATION GRADING SCHEMES **Abbreviations** **Back to TOC**	
ACPM (2008)	Not applicable

<table>
<tr><td>AUA (2009)</td><td>Not applicable</td></tr>
<tr><td>USPSTF (2008)</td><td>
What the USPSTF Grades Mean and Suggestions for Practice
<table>
<tr><th>Grade</th><th>Grade Definitions</th><th>Suggestions for Practice</th></tr>
<tr><td>A</td><td>The USPSTF recommends the service. There is high certainty that the net benefit is substantial.</td><td>Offer or provide this service.</td></tr>
<tr><td>B</td><td>The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.</td><td>Offer or provide this service.</td></tr>
<tr><td>C</td><td>The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is moderate or high certainty that the net benefit is small.</td><td>Offer or provide this service only if other considerations support offering or providing the service in an individual patient.</td></tr>
<tr><td>D</td><td>The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.</td><td>Discourage the use of this service.</td></tr>
<tr><td>I Statement</td><td>The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</td><td>Read "Clinical Considerations" section of USPSTF Recommendation Statement (see "Major Recommendations" field). If offered, patients should understand the uncertainty about the balance of benefits and harms.</td></tr>
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USPSTF Levels of Certainty Regarding Net Benefit

Definition: The U.S. Preventive Services Task Force defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net
</td></tr>
</table>

benefit of a preventive service.

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. The conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: • The number, size, or quality of individual studies • Inconsistency of findings across individual studies • Limited generalizability of findings to routine primary care practice • Lack of coherence in the chain of evidence As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: • The limited number or size of studies • Important flaws in study design or methods • Inconsistency of findings across individual studies • Gaps in the chain of evidence • Findings that are not generalizable to routine primary care practice • A lack of information on important health outcomes More information may allow an estimation of effects on health outcomes.

COMPARISON OF METHODOLOGY
Click on the links below for details of guideline development methodology

ACPM (2008)	AUA (2009)	USPSTF (2008)
All three groups performed searches of electronic databases to collect and select the evidence; USPSTF also performed hand-searches of published literature (primary and secondary sources). USPSTF is the only group to provide details		

regarding the evidence collection/selection process, citing date ranges that were searched, search terms used, and inclusion/exclusion criteria applied. The USPSTF guideline differs from the other guidelines in that a targeted evidence review was prepared by the Agency for Healthcare Research and Quality (AHRQ) staff for use in the development of the guideline. Methods used to assess the quality and strength of the evidence differ, with ACPM using subjective review and USPSTF expert consensus. AUA does not specify any method(s) used. Methods used to analyze the evidence differ somewhat as well. A basic review was done by ACPM, a review of published meta-analyses was performed by AUA, and a systematic review with evidence tables was performed by USPSTF. USPSTF is the only group to describe the evidence analysis process.

The recommendation formulation process was similar in that AUA and USPSTF utilized expert consensus; USPSTF also used balance sheets. ACPM does not state any method(s) used to formulate the recommendations. AUA and USPSTF provide a description of the process. USPSTF is the only group to rate the strength of the recommendations according to a scheme. With regard to issues of cost-effectiveness, ACPM reviewed published cost analyses. A form of peer review was used by all three groups as a method of guideline validation; AUA and USPSTF provide a detailed description of the process. An additional method of guideline validation, comparison with guidelines from other groups, was also used by ACPM and USPSTF. In addition to reviewing each other's guidelines, ACPM and USPSTF also reviewed recommendations from the AUA, the American Cancer Society, the American Academy of Family Physicians, and the American College of Physicians. ACPM also reviewed recommendations made by the Institute for Clinical Systems Improvement and the Canadian Task Force on the Periodic Health Examination; USPSTF reviewed recommendations made by the American Medical Association.

SOURCE(S) OF FUNDING **Abbreviations** **Back to TOC**	
ACPM (2008)	American College of Preventive Medicine
AUA (2009)	American Urological Association, Inc.
USPSTF (2008)	United States Government

BENEFITS AND HARMS
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Benefits	
ACPM (2008)	Benefits of screening include early detection and treatment of potentially curable stage of prostate cancer (i.e., better chances of survival with localized disease) and reassurance of being at low risk of cancer. **Subgroups Most Likely to Benefit** Men with a first-degree relative (e.g., father, brother) with prostate cancer and African-American men are at higher risk of both developing and dying from prostate cancer.
AUA (2009)	• Improvement in prostate cancer detection while minimizing unnecessary prostate biopsies • Reduction in the morbidity and mortality associated with prostate cancer, including bone pain, inanition, anemia, ureteral obstruction, and bone fractures • Improved decision-making regarding the best use of serum prostate-specific antigen for prostate cancer early diagnosis, staging, and treatment follow-up of prostate cancer
USPSTF (2008)	**Benefits of Detection and Early Treatment** • In men younger than age 75 years, the USPSTF found inadequate evidence to determine whether treatment for prostate cancer detected by screening improves health outcomes, compared with treatment after clinical detection. • In men age 75 years or older, the USPSTF found adequate evidence that the incremental benefits from treatment for prostate cancer detected by screening are small to none.
Harms	
ACPM (2008)	Both screening and treatment can be harmful: • A false positive result may lead to increased anxiety and having to experience the discomfort and possible complications associated with biopsy (e.g., pain, hematospermia/hematuria, and infection). • Prostate cancer may be slow growing and may never advance or progress to cause significant disease or death. Treatment can cause both short- and long-term side effects (e.g., pain, urinary incontinence, and impotence). • Men who received false-positive PSA test results reported having thought and worried more about prostate cancer despite receiving a negative follow-up (prostate biopsy) result. Thus, screening may cause undesirable mental health consequences. • False reassurance from a normal test (false negative), leading to a

	delayed diagnosis of prostate cancer.
AUA (2009)	• Prostate cancer screening leads to overdetection and overtreatment of some patients. • Using a lower threshold prostate-specific antigen (PSA) value for all men improves the sensitivity of PSA and the likelihood of detecting cancers, including some aggressive tumors that are present at PSA levels below 4.0 ng/mL, but also risks the detection of clinically-insignificant tumors. • In most instances, a positive test leads to a transrectal ultrasound and prostate biopsy. The risks of biopsy are small but not insignificant. Significant bleeding and infection occur in 1% to 4% of patients who undergo biopsy. • Although the psychological stress of diagnosis alone cannot be overlooked, most of the morbidity associated with PSA testing is related to the treatment procedures currently available to those found to have prostate cancer. In men with clinically significant prostate cancers, complications associated with treatment are most often considered acceptable if the treatment prolongs life or reduces morbidity from the disease. In men who harbor indolent disease or disease that is not likely to become symptomatic during the patient's lifetime, however, any morbidity from treatment likely lowers quality of life and should be considered a potential harm associated with PSA testing. Problems include urinary, bowel, and erectile dysfunction, as well as emotional distress and anxiety due to a cancer diagnosis and subsequent decision making and treatment.
USPSTF (2008)	**Harms of Detection and Early Treatment** • The USPSTF found convincing evidence that treatment for prostate cancer detected by screening causes moderate- to-substantial harms, such as erectile dysfunction, urinary incontinence, bowel dysfunction, and death. These harms are especially important because some men with prostate cancer who are treated would never have developed symptoms related to cancer during their lifetime. • There is also adequate evidence that the screening process produces at least small harms, including pain and discomfort associated with prostate biopsy and psychological effects of false-positive test results.

CONTRAINDICATIONS
Abbreviations

Back to TOC	
ACPM (2008)	Not stated
AUA (2009)	Free serum prostate-specific antigen is altered by hemodialysis and should not be used for screening in these patients.
USPSTF (2008)	Not stated

Abbreviations
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ACPM, American College of Preventive Medicine

AUA, American Urological Association

DRE, digital rectal examination

ERSPC, European Randomised Study of Screening for Prostate Cancer

PSA, prostate specific antigen

PSADT, PSA doubling time

PSAV, PSA velocity

TZPSAD, PSA density of the transition zone

USPSTF, U.S. Preventive Services Task Force

This synthesis was prepared by NGC on December 28, 1998 and has been revised a number of times. The most current version of this synthesis incorporates new guidelines from UMHS and removes recommendations of the American Urological Association (2000) and Singapore Ministry of Health (2000). The information was verified by UMHS on August 23, 2005. This synthesis was updated on December 6, 2007 to remove recommendations from USPSTF. This synthesis was revised on June 13, 2008 to add ACPM recommendations. The information was verified by ACPM on July 17, 2008. This synthesis was revised in October 2008 to add USPSTF recommendations in March 2009 to remove recommendations from ACS and most recently in March 2010 to remove UMHS recommendations and add AUA recommendations. The information was verified by AUA on April 12, 2010.

Internet citation: National Guideline Clearinghouse (NGC). Guideline synthesis: Screening for prostate cancer. In: National Guideline Clearinghouse (NGC) [Web site]. Rockville (MD): 1998 Dec 28 (revised 2010 May). [cited YYYY Mon DD]. Available: http://www.guideline.gov.

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